

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/001639

International filing date (day/month/year)
15.04.2004

Priority date (day/month/year)
15.04.2003

International Patent Classification (IPC) or both national classification and IPC
C07C29/42, C07C33/04, C07C31/20, C07C33/044, C07C33/035

Applicant
JOHNSON MATTHEY PLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/001639

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/001639

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-10
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-10
Industrial applicability (IA)	Yes: Claims	1-10
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

- D1: WO 02/094741 A (CARREIRA ERICK MORAN ; ADGER BRIAN MICHAEL (GB); ICI PLC (GB)) 28 November 2002 (2002-11-28)
- D2: FRANTZ D E ET AL: "FACILE ENANTIOSELECTIVE SYNTHESIS OF PROPARGYLIC ALCOHOLS BY DIRECT ADDITION OF TERMINAL ALKYNES TO ALDEHYDES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 122, 1 March 2000 (2000-03-01), pages 1806-1807, XP000931149 ISSN: 0002-7863
- D3: BOYALL D ET AL: "Enantioselective addition of 2-methyl-3-butyne-2-ol to aldehydes: preparation of 3-hydroxy-1-butyne" ORGANIC LETTERS, ACS, WASHINGTON, DC, US, vol. 2, no. 26, 28 November 2000 (2000-11-28), pages 4233-4236, XP002207131 ISSN: 1523-7060
- D4: BURK M J ET AL: "Highly enantioselective hydrogenation of beta-keto esters under mild conditions" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 117, no. 15, 19 April 1995 (1995-04-19), pages 4423-4424, XP002207132 ISSN: 0002-7863
- D5: BACH J ET AL: "Stereoselective Reduction of Unsaturated 1,4-Diketones. A Practical Route to Chiral 1,4-Diols" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 38, no. 6, 10 February 1997 (1997-02-10), pages 1091-1094, XP004033941 ISSN: 0040-4039
- D6: WU K-M ET AL: "Structural effects on $\Delta 1,5$ -sigmatropic hydrogen shifts of vinylallenes" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 55, no. 14, 6 July 1990 (1990-07-06), pages 4381-4392, XP002207137 ISSN: 0022-3263
- D7: US-A-5 110 966 (EVANS JONATHAN C ET AL) 5 May 1992 (1992-05-05)
- D8: DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 1990, XP002289664 retrieved from XFire accession no. RID2868854
- D9: DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 1933, XP002289665 retrieved from XFire accession no. RID636078
- D10: DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 1962, XP002289666 retrieved from XFire accession no. RID1229231

D11: DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 1989, XP002289667 retrieved from XFIRE accession no. RID2868243

1. The present application relates to a process for the production of a hydroxyalkyne by coupling reaction between acetaldehyde and a terminal alkyne, comprising the steps of (i) reacting without solvent, a terminal alkyne with a Lewis acidic metal salt in the presence of an alkanolamine ligand and a cyclic amine base to form a metal-alkyne complex and (ii) adding a solution of acetaldehyde to the metal-alkyne complex. The thermal fragmentation of the hydroxyalkyne obtained in the coupling reaction in order to yield a terminal alkyne is claimed as well.
2. D1 relates to a process for the production of a hydroxyalkyne by coupling reaction of an aldehyde and a terminal alkyne in the presence of an alkanolamine ligand, a metal triflate and an amine as a base. The production of diols using this coupling reaction and possibly a hydrogenation step is disclosed as well. The thermal fragmentation of the hydroxyalkyne obtained in the coupling reaction to yield a terminal alkyne is reported.
3. D2 relates to a process for the production of a hydroxyalkyne by coupling reaction of an aldehyde and a terminal alkyne in the presence of an alkanolamine ligand, a metal triflate and an amine as a base.
4. D3 relates to a process for the production of a hydroxyalkyne by coupling reaction of an aldehyde and a terminal alkyne in the presence of an alkanolamine ligand, a metal triflate and an amine as a base. The thermal fragmentation of the hydroxyalkyne obtained in the coupling reaction to yield a terminal alkyne is reported.
5. D4 relates to the preparation of phosphorous-containing ligands from saturated diols.
6. D5 relates to the enantioselective hydrogenation of alkyne diols to yield alkene diols and saturated diols.
7. D6 relates to a process for the production of a hydroxyalkyne by reaction of lithium acetylide and an aldehyde.
8. D7 relates to the production of hydroxyalkynes by reaction of a terminal alkyne, a

boron derivative and acetaldehyde.

9. D8 relates to a process for the production of a hydroxyalkyne by reaction of acetaldehyde and a terminal alkyne in the presence of lithium-diisopropylamid as a base.
10. D9 relates to a process for the production of a hydroxyalkyne by reaction of acetaldehyde and a terminal alkyne in the presence of potassium hydroxide, NaNH_2 or copper formate.
11. D10 relates to a process for the production of a hydroxyalkyne by reaction of acetaldehyde and a terminal alkyne in the presence of magnesium; $n\text{BuLi}$; ethyl bromide and Mg or MeI and Li .
12. D11 relates to a process for the production of a hydroxyalkyne by reaction of acetaldehyde and a terminal alkyne in the presence of $n\text{BuLi}$ or ethylmagnesium bromide.

Novelty

13. The subject-matter of claims 1-10 is novel in the sense of Art. 33(2) PCT. None of the available documents of the prior art discloses a process for the production of a hydroxyalkyne by coupling reaction between acetaldehyde and a terminal alkyne, comprising the steps of (i) reacting without solvent, a terminal alkyne with a Lewis acidic metal salt in the presence of an alkanolamine ligand and a cyclic amine base to form a metal-alkyne complex and (ii) adding a solution of acetaldehyde to the metal-alkyne complex (see paragraphs 2-12 herein).

Inventive step

14. The subject-matter of claims 1-10 cannot be considered to involve an inventive step in the sense of Art. 33(3) PCT.
 - a. The closest state of the art, D1 and D3, discloses a process for the production of a hydroxyalkyne by coupling reaction of an aldehyde and a terminal alkyne in the presence of an alkanolamine ligand, a metal triflate and an amine as a base. The production of diols using this coupling reaction and possibly a hydrogenation step is

disclosing as well. The thermal fragmentation of the hydroxyalkyne obtained in the coupling reaction to yield a terminal alkyne is reported.

- b. The problem to be solved in the application can be seen in the adaptation of the process of D1/D3 if acetaldehyde is used as the aldehyde.
- c. In view of experiment 1 in the application, the use of the conditions of the prior art (D1/D3), that means the use of a solvent in step (i), leads to bad results in the present process when acetaldehyde is used as the aldehyde. Taking into account that the present claimed process is very much affected by reactions conditions and in view that the Lewis acidic metal salt used in the process (example 2) is always zinc triflate, it does not seem obvious that the process leads to good results when any single Lewis acidic metal salt (such as for example a coordinate ferrous complex, a metalloligand of copper, ruthenium...) is employed in the process. Furthermore, not any solvent in step (ii) can be used taking into account that a metal-alkyne complex is one of the reactants in the step. In addition, there is no proof in the application showing that any alkanolamine ligand leads to good results and furthermore, no alkanolamine is used in the example which is reported as being according to the application, example 2. Hence, the technical problem is not solved and therefore an inventive step cannot be acknowledged.

Further comments

- 15. The subject-matter of claim 10 is not sufficiently disclosed, contrary to Art. 5 PCT, leading as well to lack of clarity, contrary to Art. 6 PCT. The reason therefore is that there is no indication about to which thermal fragmentation reaction is subjected the hydroxyalkyne obtained in the coupling reaction in order to yield a terminal alkyne, which could be then again the starting product of the coupling reaction. The matter for which protection is sought is not clearly defined. Hence, the claim attempts to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result and the structure of the end product in the process.
- 16. It is clear from the description on pages 2, 3 and 4 that the following features are essential to the definition of the invention:

- (1) the cyclic amine base used,
- (2) the alkanolamine ligand employed,
- (3) zinc triflate is used as the Lewis acidic metal salt and
- (3) the specific solvents which can be used in step (ii):

Since independent claim 1 does not contain these features, it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention. Furthermore, without these essential technical features, the technical problem is not solved.

- 17. The term "substantially" used at page 4, renders unclear the scope of the protection sought, contrary to Art. 6 PCT.
- 18. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D4 and D5 is not mentioned in the description, nor are these documents identified therein.
- 19. When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims.
- 20. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/GB2004/001639